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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/643,755	08/23/2000	Gijs van Rooijen	9369-153/MG	1008

1059 7590 09/03/2002

BERESKIN AND PARR
SCOTIA PLAZA
40 KING STREET WEST-SUITE 4000 BOX 401
TORONTO, ON M5H 3Y2
CANADA

EXAMINER

HELMER, GEORGIA L

ART UNIT	PAPER NUMBER
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1638

DATE MAILED: 09/03/2002

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/643,755

Applicant(s)

VAN ROOIJEN ET AL.

Examiner

Ashwin Mehta

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 July 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-28 is/are pending in the application.
- 4a) Of the above claim(s) 24-28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Restriction election

1. The Office acknowledges the receipt of Applicant's restriction election, Paper No. 11, filed 26 July 2002. Applicant elects Group I claims 1-23 without traverse. Claims 1-28 are pending. Claims 24-28 are nonelected. Claims 1-23 are examined in the instant application. This restriction is made FINAL.

Specification

2. Applicant is required to update the status (pending, allowed, etc.) of all parent priority applications in the first line of the specification. The status of all citations of US filed applications in the specification should also be updated where appropriate.

Sequence Listing

3. Applicant's CRF and paper sequence listing have been entered.

Information Disclosure Statement

4. The information disclosure statement filed 23 January 2001 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the names and dates of all US and foreign patent documents are not included. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all

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certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C (1).

Claim Rejections - 35 USC § 112, second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, "chimera" is unclear. IT is unclear whether the components which make up the nucleic acid are chimeric to each other, of whether the nucleic acid I chimeric to the plant cell. Is the sequence chimeric? Or the molecule?

- In a)-1) and 2), what are the nucleic acid sequences operatively linked to?
- In step b), expression of the desired sequence is lacking.

Claim 1 is an incomplete method claim because the final step of the method (obtaining seed) does not produce the desired product (producing chymosin in a plant seed).

Claim 3 has improper claim dependency, as a claim cannot depend on itself.

In claim 4, Total seed protein" lacks antecedent basis. Suggested language to clarify this claim is "wherein the seed contains at least 0.5% (w/w) chymosin in".

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In claim 8, "signal" should be inserted after "PR-S".

In claim 11, "obtainable" should be changed to "obtained".

In claim 12, "codon usage" lacks antecedence basis.

In claim 13, it is unclear what the parentheticals mean. Are they further limitations? Or examples?

In claim 17, Applicant should clarify that the plants of step (e) are not plants grown from the seed of step (d), but are plants that produced the seeds of step (d).

In claim 18, "said seed" is unclear. Which seed? the progeny? or that of step (c)?

Claims 19-23 are dependent on claim 1, which is a method of producing, whereas 19-23 are set forth as a method of purification.

Claim 19 (ii), "fraction" is unclear. Does this mean a small part? Or a component part? Or a phase such as the aqueous fraction?

Clarification and/or correction are required.

Claim Rejections - 35 USC § 112, first paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 18-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of isolating chymosin from an aqueous

fraction from *Brassica napis* seed, does not reasonably provide enablement for isolating chymosin from any fraction from any plant seed.

The specification does not enable any person skilled in the art to which pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. .

Applicant's invention involves a method for the commercial production of chymosin involving recombinant expression of chymosin plant seeds, and a method for the isolation of chymosin from the seeds.

The enablement issues are any seed and any fraction of the plant seed.

Re any seed: Applicant claims method of isolated chymosin from seed of any transgenic plant (produced by claim 1). Applicant teaches a method of isolation from *Brassica napis* seed. Protein isolation and purification take into account two kinds of factors: (i) separation of the protein of interest from a particular biological source, and (ii) the biochemical properties of the particular protein. It is well known in the art that plant seed development and the location and composition of the various stored components vary among seeds of different species. (Buchanan, et al. *Biochemistry & Molecular Biology of Plants* (2000) American Society of Plant Physiologists, Rockville Md 20855, pages 1024-1028, and Table 19.2). It is unpredictable that a method of enzyme purification developed for *Brassica napis* seed, composed of 48% oil, 19% carbohydrate, and 21% protein, with the major storage organ being the cotyledons, would function as desired for maize seed, with 5% oil, 80% carbohydrates, and 10% protein, with the major storage organ being the endosperm, or for any other plant, with

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reasonable expectation of success. Applicant has provided no guidance on how to predictably eliminate inoperable embodiments from a virtually ad infinitum of possibilities other than by random trial and error, which is excessive experimentation and an undue burden.

Re any fraction: Applicant claims a method of isolating chymosin from plant seed involving crushing the plant seed, contacting the crushed seed or a fraction thereof with a protein binding resin, and recovering chymosin from the protein binding resin.

Applicant teaches an aqueous fraction. It is well known in the art that in order to isolate a desired protein from a particular fraction, that particular protein has to be physically present in that fraction. It is unpredictable that any fraction would function as desired in the claimed invention. As further evidence, claim 19 recites an aqueous fraction.

In view of the breadth of the claims (any plant seed, and any fraction), the lack of guidance in the specification, undue trial and error experimentations would be required to enable the invention as commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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10. Claims 1-7, 11, and 13-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Willmitzer et al (WO 92/01042) (specification, p 3). Willmitzer teaches a method for the production of chymosin in a plant seed comprising introducing into tobacco and potato plant cells a chimeric nucleic acid sequence comprising a seed-specific phaseolin promoter, a nucleic acid sequence encoding pro-peptide chymosin, and a terminator, then growing the plant until it sets seeds and obtaining chymosin-containing seeds (Abstract, p 4, 5, 10 and 13). Seeds obtained from the transgenic plants are tested to assure that the gene of interest is present. The expressed enzyme can be isolated from the seed (p 3). Willmitzer further teaches including a plant signal sequence (p 5). The pro-chymosin of Willmitzer appears to a mammalian chymosin obtainable from a bovine, sheep, or goat source (p13), since these are the only known nature sources of chymosin (specification, p.1). Since the method of Willmitzer is the same as Applicant's method, and teach the same promoter as preferred by Applicant, the percentage yields would have been an inherent property of the DNA construct used. If Applicant's percentage yields are different from that of Willmitzer, it is suggested that Applicant amend the claims and include specific structures such which would account for this difference.

Willmitzer further teaches a method of isolating chymosin by crushing (p 12, line10) plant tissue, fractionating the resulting product (p 12, lines 9-15), contacting this product with a protein binding resin (p 12, lines 20-25).

Accordingly Willmitzer anticipates the claimed invention.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. Claims 1-8, 10, 11, and 13-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Willmitzer (WO 92/01042) as applied to claims 1-7, 11, and 13-19 above, and further in view of Applicants admitted prior art. The teachings of Willmitzer are discussed supra.

While Willmitzer teaches the inclusion of a plant signal sequence and terminator in a chimeric construct, Willmitzer does not specifically teach a tobacco PR-S signal sequence and phaseolin terminator. However, the inclusion of a heterologous signal sequence and terminator in a chimeric construct was notoriously well known in the art, as evidenced by the numerous examples set forth by Willmitzer (p. 5) as well as by Applicant (p. 9 and 12). Applicant's admitted prior art indicates that a tobacco PR-S signal sequence and phaseolin terminator, as well as their biological properties, were also known at the time the invention was made (p. 9 and 12). Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize any of the known plant signal sequences and terminators of the prior art, including the claimed tobacco PR-S signal sequence and phaseolin terminator, for their known biological properties, in the chimeric construct for expressing the chymosin of Willmitzer without any surprising or unexpected results. One skilled in the art would

have been motivated to generate the claimed invention with a reasonable expectation of success.

While it is known that seeds can be fractionated into three fractions (oil, aqueous, and insoluble) based on water solubility, Willmitzer does not teach contacting the aqueous fraction with the protein binding resin. However it is well known that proteins are polyelectrolytes, having multiple positive and negative-charged ionic groups. And that given the phases of oil, water and insoluble, proteins would be found in the aqueous phase. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to take the aqueous phase, for its known biochemical properties, and contact it with the protein binding resin of Willmitzer, to generate the claimed invention, without any surprising or unexpected results.

While Willmitzer teaches methods of protein isolation using a protein binding resin, he does not specifically teach hydrophobic interaction resins. However, it is well known that proteins are amphipathic molecules, having both strongly polar and strongly nonpolar groups. Applicant's admitted prior art indicates that hydrophobic interaction resins and ion-exchange resins were known at the time the invention was made (p. 23, 24, specification). Accordingly it would have been prima facie obvious to one of ordinary skill in the art of the time the invention was made to contact the aqueous fraction, with a hydrophobic interaction resin, for its known biochemical and physical properties, to generate the claimed invention, without any surprising or unexpected results.

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While Willmitzer teaches methods of protein isolation using a protein binding resin, he does not specifically teach ion-exchange resins. However it is well known that proteins are polyelectrolytes, having multiple positive and negative-charged ionic groups. Accordingly it would have been prima facie obvious to one of ordinary skill in the art of the time the invention was made to contact the aqueous fraction, with an ion-exchange resin, for its known biochemical and physical properties, to generate the claimed invention, without any surprising or unexpected results.

13. Claims 1-8, and 10-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Willmitzer (WO 92/01042) as applied to claims 1-8, 10, 11, and 13-23 above, and further in view of Adang et al (US 5,380,831). While Willmitzer does not teach optimizing the codon usage of the nucleic acid sequence encoding chymosin for use in plants, such practice was well known in the prior art, as evidenced by Adang. Adang teaches expressing a heterologous protein (Bacillus thuringiensis toxin gene) in plants utilizing codons preferred in highly expressed plant proteins. Accordingly, one skilled in the art would have been motivated at the time the invention was made to express a heterologous protein such as chymosin using plant preferred codons for the purpose of optimizing expression of the protein of interest with a reasonable expectation of success.

Remarks

14. SEQ ID NO: 1 is free of the prior art.

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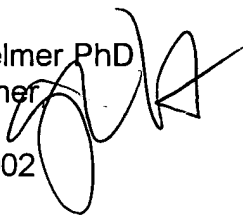
15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Georgia L. Helmer whose telephone number is 703-308-7023. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 703-306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Georgia L. Helmer PhD
Patent Examiner
Art Unit 1638
August 29, 2002



Phuong Bui
PHUONG T. BUI
PRIMARY EXAMINER 8/29/02